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Enantioselective Total Synthesis of (−)-Zampanolide, a Potent Microtubule-Stabilizing Agent

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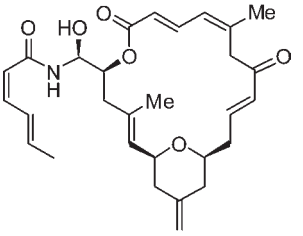
ABSTRACT



(-)-Zampanolide **1**

An enantioselective total synthesis of zampanolide has been accomplished using a novel DDQ/Brønsted acid promoted cyclization as the key reaction. The synthesis features cross-metathesis to construct the trisubstituted olefin and a ring-closing metathesis to form the macrolactone. The final *N*-acyl aminal formation was stereoselectively accomplished by an organocatalytic reaction.

The isolation of taxol in the 1970s and subsequent decade-long studies led to the approval of paclitaxel as an important anticancer drug.[1] Paclitaxel inhibits cell division by stabilizing microtubule assembly.[2] Since the discovery of this unique mechanism of action, the search for new agents has become the subject of immense interest. In recent years, epothilones and discodermolide-based antitumor therapeutics have received significant attention.[3] Also, laulimalide and pelorusides were identified as an exciting new generation of microtubule-stabilizing agents.[4] Both laulimalide and pelorusides have exhibited intriguing synergistic effects with taxol, maintained potent activity against taxol-resistant cell lines, and are not substrates for P-glycoprotein-mediated drug efflux pumps.[5,6]

More recently, Northcote, Miller, and co-workers reported that (−)-zampanolide **1** (Figure 1), a 20-membered macrolide, also possesses potent microtubule-stabilizing properties.[7]

Zampanolide (**1**) was originally isolated by Tanaka and Higa from the marine sponge *Fasciospongia rimosa* in Okinawa in 1996.[8] More recently, (−)-zampanolide **1** was isolated from a Tongan marine sponge, *Cacospongia mycofijiensis*, and reported to block cell division in the G2/M of the cell cycle.[7] Uenishi and co-workers reported the potent cytotoxic activity of (−)-zampanolide against SKM-1 and U937 cell lines with IC_{50} values of 1.1 and 2.9 nM, respectively.[9] Furthermore, it is potent against HL-60, 1A9 cells, and especially against A2780AD, which is quite resistant to paclitaxel.[7] Zampanolide's natural abundance is very scarce which has resulted in only limited biological studies. Zampanolide possesses a unique unsaturated macrocyclic structural feature containing only three stereogenic centers and a chiral *N*-acyl aminal side chain.

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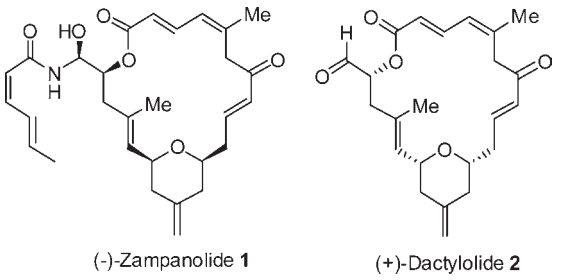

Figure 1. (−)-Zampanolide **1** (natural form) and (+)-dactylolide **2** (enantiomer of natural form).

The chemistry and biology of zampanolide have attracted much synthetic attention. Smith and co-workers achieved the first total synthesis of (+)-zampanolide, the unnatural antipode, in 2001.[10] Subsequently, both Hoye et al. in 2003[11] and Uenishi et al.[9] in 2009, reported the total synthesis of natural (−)-zampanolide. These syntheses established that the natural (−)-zampanolide core is the opposite enantiomer of the related natural product (+)-dactylolide (**2**). Dactylolide displayed only modest cytotoxicity. Since its discovery by Riccio and co-workers in 2001,[12] a number of total syntheses[13−19] and a synthetic approach to (+)-dactylolide have been reported.[20] It appears that the *N*-acyl aminal side chain of (−)-zampanolide is important for its potent cytotoxic properties. The key *N*-acylation reaction typically[9] provided only a 12% yield of zampanolide along with its epimer and *N*-acylated product, suggesting that an improvement is necessary for the synthesis of structural variants. Herein, we report an enantioselective synthesis of (−)-zampanolide that can be amenable to the synthesis of *N*-acyl aminal derivatives.

Our synthetic strategy for (−)-zampanolide (**1**) is shown in Figure 2. We planned to synthesize the macrocyclic core in a convergent manner to prepare a variety of structural analogs. Our strategic bond disconnection of the sensitive *N*-acyl aminal side chain at C20 provides macrolactone **3**, which can be formed from alcohol **4** and acid **5** by esterification followed by ring-closing metathesis. A similar RCM strategy was first employed by Hoye and

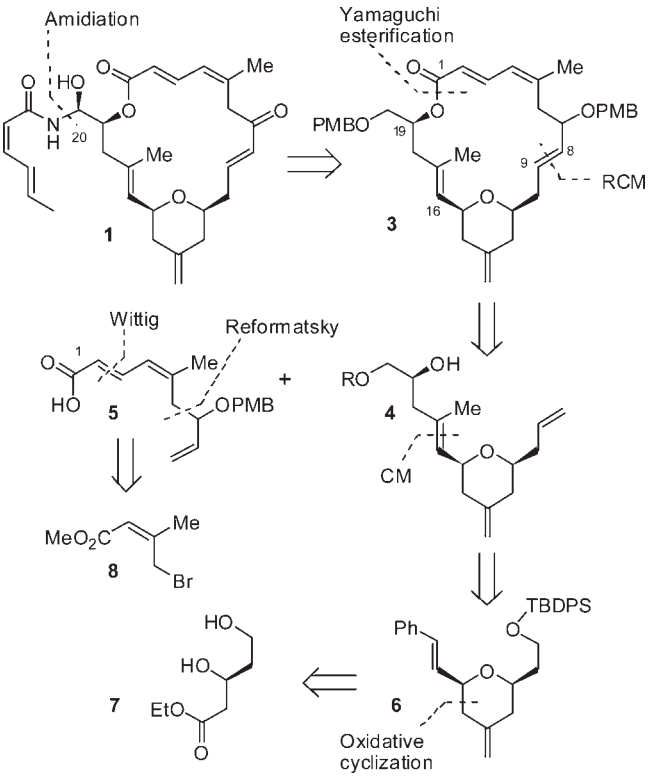

Figure 2. Synthetic plan for (−)-zampanolide **1**.

Hu.[11] The trisubstituted olefin in **4** would be installed by a cross metathesis of **6**. The tetrahydropyran ring **6** would be constructed by an oxidative cyclization reaction of a cinnamyl ether derived from β-hydroxy ester **7**. The polyene carboxylic acid **5** would be assembled by a Reformatsky reaction with γ-bromo unsaturated ester **8** followed by Wittig olefination of the corresponding aldehyde.

As shown in Scheme 1, the synthesis commenced with known ester **7**, which was readily prepared with excellent enantioselectivity using Noyori hydrogenation as the key step.[21] Selective protection of the primary alcohol as a TBDPS ether provided **9**. Etherification of the secondary alcohol with *tert*-butyl cinnamyl carbonate in the presence of a catalytic amount of $Pd(PPh_3)_4$ afforded cinnamyl ether **10** in 73% yield. The ethyl ester **10** was converted to allylsilane **11** by employing a modified procedure of Narayanan and Bunnelle to provide **11** in 81% yield.[22] Our subsequent plan was to carry out an oxidative Sakurai type cyclization to construct the 4-methylenetetrahydro-2*H*-pyran ring stereoselectively. For this transformation, we initially explored an oxidative cyclization reaction with DDQ, as benzylic/allylic ethers have been converted to carbocation intermediates using DDQ with or without Lewis acids by Mukaiyama and Hayashi,[23] She et al.,[24]

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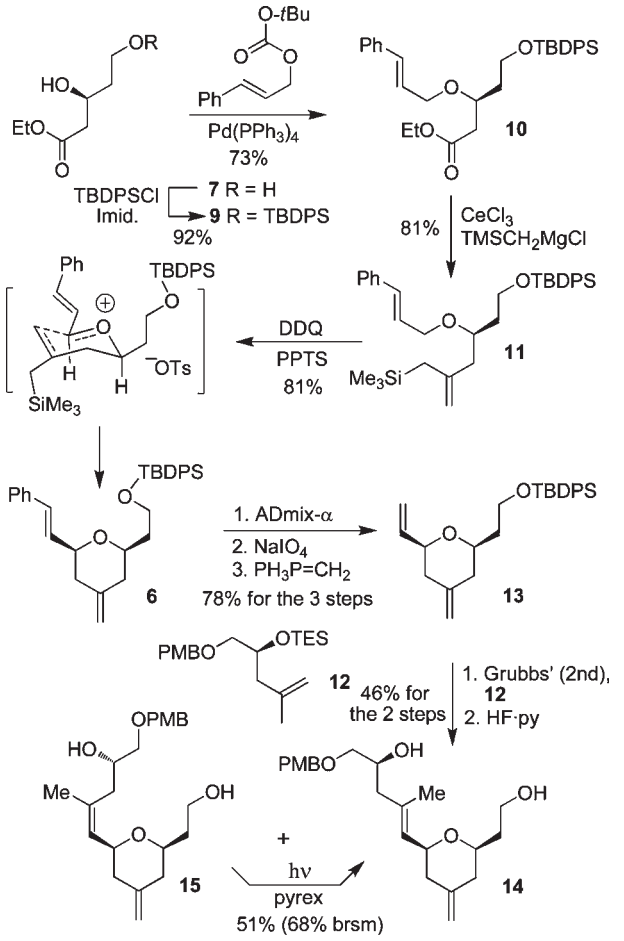
Scheme 1. Synthesis of Tetrahydropyran **14**

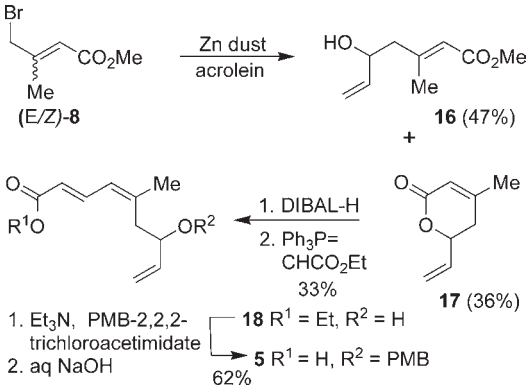


and Floreancig et al.[25] The reaction with DDQ at −40 °C for 3 days resulted in only 30−35% desired product **6** along with unidentified side products possibly due to the presence of the allylsilane functionality. The same reaction in the presence of a variety of Lewis acids also provided similar results. However, oxidative cyclization with DDQ in the presence of a mild Brønsted acid such as PPTS provided the best results. Reaction of **11** with 1.5 equiv of DDQ and 1.5 equiv of PPTS at −38 °C in acetonitrile for 3 h afforded **6** in 81% yield as a single diastereomer (by ^{1}H NMR analysis). The NOESY data fully corroborated the depicted *cis*-stereochemistry of **6**. Presumably, the cyclization proceeded through a Zimmerman−Traxler transition state where all substituents are equatorially oriented.[26]

Our synthetic strategy then called for the elaboration of the *E*-trisubstituted olefin in **4** by a cross-metathesis reaction. The corresponding olefin substrate **12** was obtained in an optically active form by opening a PMB-protected glycidyl derivative with isopropenylmagnesium bromide followed by protection of the resulting alcohol as TES-ether. Our attempted cross-metathesis of **6** with **12** under a variety of conditions did not provide any cross-metathesis product. Assuming the lack of reactivity of the styrene chain, we planned to convert the styrene chain into a methylene chain. This was achieved by selective dihydroxylation of the styrene chain with ADmix-α followed by diol cleavage with $NaIO_4$ to provide the corresponding aldehyde as described by Smith and Dong.[27] Wittig olefination of the resulting aldehyde with methylene phosphorane afforded **13** in 78% yield (3 steps). Cross-metathesis[28] of **13** with **12** using Grubbs' second generation catalyst (10 mol %) in CH_2Cl_2 at reflux for 9 h provided an *E*/*Z* olefin mixture (1.7:1) in 57% yield. The mixture was treated with HF·py to remove all silyl groups. The resulting alcohols were separated by silica gel chromatography. Photochemical isomerization of the *Z*-isomer **15** provided a 51% yield (68% brsm) of trisubstituted olefin **14**.

The synthesis of polyene carboxylic acid **5** is shown in Scheme 2. Allyl bromide **8** was prepared as an *E*/*Z* mixture (1.3:1) using the procedure of Fallis and Lei.[29] Reformatsky reaction of the mixture of bromides **8** with acrolein resulted in allylic alcohol **16** (47% yield) and unsaturated δ-lactone **17** (36% yield) after separation by silica gel chromatography. DIBAL-H reduction of **17** followed by Wittig reaction with (carbethoxymethylene)triphenylphosphorane afforded allylic alcohol **18**. Protection of the resulting alcohol as a PMB-ether followed by saponification of the ester provided acid **5** in 62% yield (2 steps).

Scheme 2. Synthesis of Polyene Carboxylic Acid **5**



The synthesis of macrolactone **3** is shown in Scheme 3. The primary alcohol in **14** was selectively oxidized with TEMPO in the presence of $PhI(OAc)_2$. The resulting aldehyde was subjected to Wittig olefination with methylenetriphenylphosphorane to provide **19** in 60% yield (2 steps). Esterification of acid **5** with alcohol **19** under Yamaguchi conditions using 2,4,6-trichlorobenzoyl chloride

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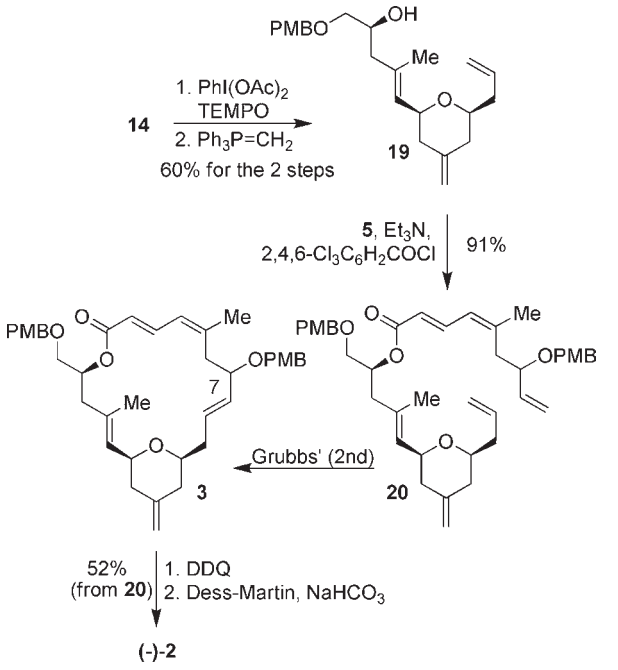
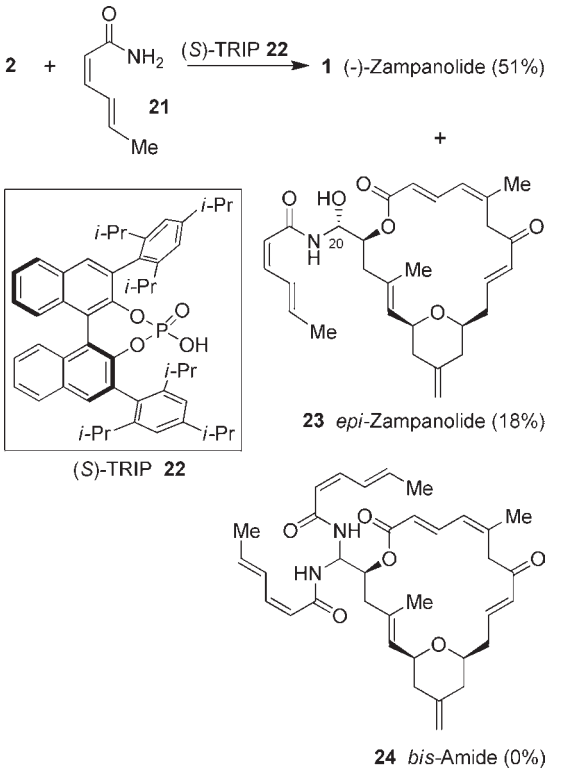
Scheme 3. Synthesis of (−)-**2**



Scheme 4. Synthesis of (−)-Zampanolide



and DMAP furnished ester **20** in 91% yield. Ring-closing metathesis using Grubbs' second generation catalyst (12 mol %) in benzene at 60 °C for 20 h afforded **3** as a mixture (1:1) of diastereomers at the C7 chiral center. Removal of both PMB-ethers by treatment with DDQ provided the corresponding diol. Dess−Martin oxidation of the diol furnished (−)-**2**, the unnatural antipode of dactylolide (52% for the 3 steps).

The conversion of (−)-**2** to (−)-zampanolide **1** required the addition of a carboxamide to the aldehyde to form a *N*-acyl aminal. Such direct addition in one previous synthesis[9] afforded only a 12% yield of (−)-zampanolide, 12% yield of epimeric product **23**, and 16% yield of *bis*-amide **24**. In an effort to improve this reaction, we investigated Brønsted acid-catalyzed *N*-acyl aminal formation under a variety of reaction conditions. In one of our initial successful attempts, reaction of (−)-**2** with carboxamide **21** in the presence of diphenylphoshoric acid clearly provided a mixture of all three products, (−)-zampanolide, *epi*-zampanolide, and *bis*-amide **24**, although analysis of the mixture showed that (−)-zampanolide formation was favored slightly. Encouraged by this result, we then investigated *N*-acyl aminal formation between aldehyde (−)-**2** and amide **21** in the presence of matched chiral phosphoric acid (*S*)-TRIP[30,31] (**22**, 20 mol %) at 23 °C for 12 h. These reaction conditions provided excellent chemoselectivity toward monoaddition, and the formation of *bis*-amide **24** was not observed. The reaction furnished (−)-zampanolide in 51% yield and *epi*-zampanolide **23** in 18% yield after separation/purification by HPLC (Scheme 4). We have also investigated the corresponding mismatched reaction with (*R*)-TRIP; however, this reaction afforded a 1:1 mixture of (−)-**1** and *epi*-**1**. Again, the formation of *bis*-amide **24** was not observed. The spectral data (^{1}H NMR and ^{13}C NMR) of synthetic **1** ($[\alpha]^{22}_D$ −94, *c* 0.08, CH_2Cl_2) is in agreement with that of natural zampanolide (Lit.[8] $[\alpha]^{22}_D$ −101, *c* 0.12, CH_2Cl_2).

In summary, we have accomplished an enantioselective synthesis of (−)-zampanolide. The synthesis features a novel intramolecular oxidative cyclization reaction, a cross-metathesis reaction to construct a trisubstituted olefin, a ring-closing metathesis to form a highly functionalized macrolactone, and a chiral phosphoric acid catalyzed stereoselective *N*-acyl aminal formation that stereoselectively furnished (−)-zampanolide and no bis-amide by-product. The present synthesis is amenable to the synthesis of structural variants of (−)-zampanolide, and further investigations of important analogs are in progress.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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